

DATA EVALUATION RECORD

RPA 407213 (FENAMIDONE)

Study Type: §82-1b, Subchronic Oral Toxicity Study in Mice

Work Assignment No. 4-01-155C (MRID 45386027)

Prepared for
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TXR#: 0050175**DATA EVALUATION RECORD****STUDY TYPE:** 90-Day Oral Toxicity [feeding] - mouse; OPPTS 870.3100b [§82-1b]; OECD 408.**PC CODE:** 046679**DP BARCODE:** D278089**SUBMISSION NO.:** S603761**TEST MATERIAL (PURITY):** RPA 407213 (Fenamidone; 98.9% a.i.)**SYNONYMS:** (S)-3,5-dihydro-5-methyl-2-methylthio-5-phenyl-3-phenylamino
4H-imidazol-4-one**CITATION:** Bigot, D. (1997) 90-Day Toxicity Study in the Mouse by Dietary Administration.
Rhône-Poulenc Agro, Sophia Antipolis Cedex, France. Laboratory Report No.:
SA 96183, September 5, 1997. MRID 45386027. Unpublished.**SPONSOR:** Aventis CropScience, 2 T.W. Alexander Dr., Research Triangle Park, NC**EXECUTIVE SUMMARY:** In a subchronic oral toxicity study (MRID 45386027), RPA 407213 (fenamidone; 98.9% a.i., Lot/batch #MDA 9607) was administered in the diet to 10 C57 Black 10J mice/sex/group at dose levels of 0, 50, 200, 1000, or 5000 ppm (equivalent to 0/0, 11.31/13.70, 44.49/54.13, 220.17/273.86, and 1064.25/1375.17 mg/kg bw/day in the males/females) for at least 90 days. Food efficiency was not determined, and no hematological parameters were examined. There were no effects of treatment on mortality, body weights, body weight gains, or food consumption.

Changes in organ weights, gross pathology, histopathology, and clinical chemistry indicated slight treatment-related effects on the **liver**. In the males, relative (to brain) liver weight was increased (incr. 9%; $p \leq 0.01$) at 1000 ppm; and absolute, relative (to body), and relative (to brain) liver weights were increased (incr. 14-16%; $p \leq 0.01$) at 5000 ppm. In the 200 to 5000 ppm males, dose-dependent increases were observed in the incidence of pale liver (5/10 to 7/10 treated vs 3/8 controls) and hepatocellular microvacuolation (6/9 to 8/10 treated vs 4/8 controls).

In the females, prominent lobulation was noted at 1000 and 5000 ppm (1/10 and 1/9 treated vs 0/10 controls), and acute inflammatory cell infiltrate was observed at 5000 ppm (1/9 treated vs 0/10 controls). Additionally, in the 5000 ppm females, cholesterol was decreased (decr. 29-47%; $p \leq 0.05$).

Opacity was observed in the **eyes** of one 5000 ppm female (vs 0/10 controls). A dose-dependent increase in the incidence of diffuse corneal opacity (1/9 to 4/10 treated vs 0/8 controls) was observed in the 150 to 5000 ppm males; however, in the absence of correlative changes in

histopathology, this finding is considered equivocal. Additionally at 5000 ppm, diffuse, marked axonal swelling and myelin sheath vacuolation in the **sciatic nerve** was observed in the males (1/10 treated vs 0/8 controls); and diffuse, marked atrophy of the **thymus** was observed in the females (2/9 treated vs 0/10 controls). One male in each of the treated groups had dark brown pigment-loaded macrophages in the **spleen**; these findings increased in severity (slight to moderate) with increasing dose.

The LOAEL for this study is 1000 ppm (equivalent to 220.17/273.86 mg/kg/day in the males/females) based on mild hepatotoxicity as evidenced by increased liver weights and incidences of pale liver and hepatic microvacuolation in the males and decreased cholesterol and increased incidence of prominent lobulation of the liver in the females. The NOAEL is 200 ppm (equivalent to 44.49/54.13 mg/kg/day in the males/females).

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirements for a subchronic oral toxicity study in the mouse (OPPTS 870.3100b; OECD 408).

COMPLIANCE: Signed and dated Data Confidentiality, GLP, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS**A. MATERIALS**

1. **Test material:** RPA 407213 (fenamidone)
- Description:** White powder
- Lot/Batch #:** MDA9607
- Purity:** 98.9% a.i.
- Compound Stability:** Stable in the diet for 7 weeks frozen followed by 1 week at room temperature
- CAS #:** 161326-34-7
- Structure:**

2. **Vehicle:** Diet

3. **Test animals:**
- Species:** Mouse
- Strain:** C57 Black 10J
- Age/weight at study initiation:** 6-7 weeks/19.6-23.1 g, males; 14.6-18.9 g, females
- Source:** Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield Cheshire, U.K.
- Housing:** Individually, in suspended, stainless steel, wire mesh cages
- Diet:** Certified rodent diet CT1 (E) SQCFG (SDS, Witham Essex, U.K.), *ad libitum*, except during overnight fasting prior to blood sampling.
- Water:** Filtered and softened tap water, *ad libitum*, except during overnight fasting prior to blood sampling.
- Environmental conditions:**
- | | |
|---------------------|------------------------------|
| Temperature: | 20-24°C |
| Humidity: | 40-70% |
| Air changes: | 10-15 per hour |
| Photoperiod: | 12 hours light/12 hours dark |
- Acclimation period:** 8 days

B. STUDY DESIGN

1. **In life dates** - Start: 09/11/96 End: 12/13/96
2. **Animal assignment:** Animals were selected from the middle of the weight range by an automatic procedure and were randomly assigned, stratified by weight, to the test groups presented in Table 1.

Table 1. Study design ^a

Test Group	Conc. in Diet	Dose to Animal	# Males	# Females
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	(ppm)	(mg/kg/day) M/F		
Control	0	0/0	10	10
Low	50	11.31/13.70	10	10
Mid	200	44.49/54.13	10	10
Mid-High	1000	220.17/273.86	10	10
High	5000	1064.25/1375.17	10	10

a Data were obtained from page 15 and Table 5 on page 61 of the study report.

3. Dose selection rationale - It was stated that the doses summarized in Table 1 were based on a previous study performed with CD1 mice; however, no dose rationale was provided.

4. Treatment preparation, administration, and analysis - On two occasions during the study (approximately 7 weeks apart), the required quantity of finely ground test substance was added to the diet and dry mixed to make up the test diets. Homogeneity was verified for the 50 and 5000 ppm diets from the first preparation. Stability after frozen storage for 7 weeks and subsequent room temperature storage for 1 week was determined for the 50 and 5000 ppm diets from the first preparation. Concentration analyses were determined for each dose level from each preparation.

Results - Homogeneity Analysis (range as % of nominal):

50 ppm: 93-104%

5000 ppm: 97-100%

Stability Analysis (% of nominal after 7 weeks frozen followed by 1 week at room temperature):

50 ppm: 87%

5000 ppm: 100%

Concentration Analysis (range as % of nominal):

50 ppm: 94-97%

200 ppm: 94-96%

1000 ppm: 95-96%

5000 ppm: 95-98%

The analytical data indicated that the mixing procedure was adequate and the variation between nominal and actual dosage to the animals was acceptable.

5. Statistics - The following statistical procedures were employed:

Parameter	Statistical Test
Body weights, body weight gains, food consumption, clinical chemistry, and organ weights	Bartlett's test for homogeneity of variances followed by analysis of variance (ANOVA) and Dunnett's test if variances were homogeneous or by Kruskal-Wallis and Mann-Whitney test if

variances were heterogeneous.

The levels denoting significance were $p \leq 0.05$ and $p \leq 0.01$ for each statistical comparison. In general, the statistical methods were considered appropriate. However, it was not stated that normal distribution was determined for any of the data. This assumption should be verified before proceeding with parametric analyses.

C. METHODS

1. **Observations** - Animals were checked for mortality, moribundity, and clinical signs of toxicity twice daily (once daily on weekends and public holidays). Detailed physical examinations were performed at least weekly during the treatment period.
2. **Body weight** - Each mouse was weighed prior to treatment, weekly throughout the study, and at termination. Group mean body weight gains were reported for each weekly interval during the study. Overall (weeks 0-13) body weight gains were calculated by the reviewers from the group mean body weight data.
3. **Food consumption, food efficiency, and compound intake** - Food consumption (g) was recorded weekly for each mouse. Food efficiency was not calculated. Group mean achieved test substance intake (mg/kg/day) was calculated for each week and for the overall (weeks 1-13) study.
4. **Hematology & clinical chemistry** - Blood was collected from the retro-orbital venous plexus of each surviving mouse on study days 91, 92, 93, or 94. Animals were fasted overnight prior to blood sampling (except on day 93) and were anesthetized by inhalation of isoflurane. The CHECKED (X) parameters were examined.
 - a. **Hematology** - No hematological parameters were examined.
 - b. **Clinical Chemistry**

	ELECTROLYTES		OTHER
	Calcium	X	Albumin*
	Chloride		Creatinine*
	Magnesium	X	Urea nitrogen*
	Phosphorus	X	Total Cholesterol*
	Potassium*		Globulins
	Sodium*		Glucose*
		X	Total bilirubin
	ENZYMES	X	Total protein (TP)*
X	Alkaline phosphatase (ALK)*		Triglycerides
	Cholinesterase (ChE)		Serum protein electrophores
	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		

X	Alanine amino-transferase (ALT/also SGPT)*	
X	Aspartate amino-transferase (AST/also SGOT)*	
	Sorbitol dehydrogenase*	
	Gamma glutamyl transferase (GGT)*	
	Glutamate dehydrogenase	

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

5. Urinalysis - Urinalysis, optional for 90-day oral rodent studies based on Guideline 870.3100, was not performed.

6. Sacrifice and pathology - On study days 91, 92, 93, or 94, all surviving animals were fasted overnight (except on day 93) and euthanized by exsanguination under pentobarbital anesthesia. Animals found dead or sacrificed on schedule were subjected to gross pathological examination. The CHECKED (X) tissues were collected, preserved in 10% neutral buffered formalin (except eyes, optic nerve, epididymis, and testis which were fixed in Davidson's fixative), and embedded in paraffin. The (XX) organs were weighed for all animals sacrificed on schedule.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta*	X	Brain*+
				X	
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes & optic nerve*
X	Jejunum*	X	Thymus*+		GLANDULAR
X	Ileum*			X	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroid*
X	Rectum*	X	Urinary bladder*	X	Thyroid *
XX	Liver*+	XX	Testes*+		OTHER
X	Gall bladder (not rat)*	X	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin*
	RESPIRATORY	X	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	X	Uterus*+	X	Articular surface (femoro-tibial)
X	Lung*	X	Mammary gland*		
	Nose*	X	Vagina		
	Pharynx*				
X	Larynx*				

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

+ Organ weights required for rodent studies.

Microscopic examination was performed on histological sections (stained with hematoxylin and eosin) from all tissues (except the larynx) collected from animals in the control and 5000 ppm groups and from decedents in all dose groups. Tissues from the liver, lungs, kidneys, and any

gross lesions were also examined in the intermediate dose groups. Additionally, if an effect was established at 5000 ppm, target tissues from the intermediate dose groups were examined.

II. RESULTS

A. OBSERVATIONS

1. **Clinical signs of toxicity** - Opacity was observed in the eyes of one 5000 ppm female (vs 0/10 controls). There were no other dose-dependent clinical observations.

2. **Mortality** - There were no treatment-related deaths during the study. In the controls, two males and one female died due to accidental trauma (i.e. broken neck or ruptured spinal cord). Additionally, one 200 ppm male was found dead on day 33; necropsy of this animal revealed hydrocephalus and stomach ulcer/erosion.

B. BODY WEIGHT AND WEIGHT GAIN: There were no treatment-related differences in body weights or body weight gains (Table 2). Body weights of the males were comparable to controls throughout the study. In the females, body weights were increased ($\uparrow 6\%$; $p \leq 0.05$) at 1000 ppm at day 71; however, this increase was not dose-dependent. Overall (day 1-90) body weight gains were comparable to controls in the treated males and females. The following significant ($p \leq 0.05$) differences in body weight gains were noted but were deemed unrelated to treatment because they were sporadic and/or not dose-related: (i) increased at week 7 in the 1000 and 5000 ppm males; (ii) decreased at week 8 in the 1000 and 5000 ppm males; and (iii) decreased at week 8 in the 200 ppm females.

Table 2. Mean (\pm SD) body weights and overall body weight gains (g) in mice treated with RPA 407213 in the diet for up to 90 days.^a

Study Day	Dose (ppm)				
	0	50	200	1000	5000
Males					
1	21.50 \pm 0.843	21.83 \pm 0.926	21.79 \pm 0.759	21.92 \pm 0.903	22.13 \pm 0.683
43	25.30 \pm 0.464	25.32 \pm 1.014	24.82 \pm 0.424	25.25 \pm 0.907	25.29 \pm 0.606
90	28.16 \pm 0.534	27.99 \pm 1.106	27.96 \pm 0.859	28.01 \pm 0.831	28.37 \pm 1.068
Overall (1-90) gain ^b	6.66	6.16	6.17	6.09	6.24
Females					
1	17.35 \pm 1.208	17.54 \pm 0.696	17.56 \pm 0.659	17.48 \pm 0.487	17.55 \pm 0.893
43	21.39 \pm 1.657	21.71 \pm 1.405	22.25 \pm 1.002	21.88 \pm 2.222	21.36 \pm 1.820
90	24.58 \pm 0.883	24.35 \pm 0.969	24.59 \pm 1.010	25.31 \pm 1.093	24.78 \pm 0.915
Overall (1-90) gain ^b	7.23	6.81	7.03	7.83	7.23

a Data were obtained from Table 2 on pages 39-45 of the study report; n=8-10.

b Calculated by the reviewers from the group mean body weight data presented in this table.

C. FOOD CONSUMPTION

1. **Food consumption** - There were no treatment-related differences in food consumption in the males or females. Food consumption in the treated males was comparable to controls throughout the study. In the females, food consumption was increased ($\uparrow 12\%$; $p \leq 0.05$) at 200 ppm at week 4; however, this increase was not dose-dependent and did not result in significant changes in body weights in these animals.

2. **Compound consumption** - Group mean compound intake values (mg/kg/day) for the overall study are reported in Table 1.

3. **Food efficiency** - Food efficiency was not determined.

D. BLOOD ANALYSES

1. **Hematology** - No hematological parameters were examined.

2. **Clinical chemistry** - In the treated males, all clinical chemistry parameters were comparable to controls. Cholesterol was decreased ($\downarrow 29$ -47%; $p \leq 0.05$) in the 1000 and 5000 ppm females (Table 3). There were no other dose-dependent changes in clinical chemistry.

Table 3. Mean (\pm SD) cholesterol (mmol/L) in female mice treated with RPA 407213 in the diet for up to 90 days.^a

Dose (ppm)				
0	50	200	1000	5000
0.883 \pm 0.1434	0.721 \pm 0.1475	0.774 \pm 0.1444	0.627 \pm 0.1368* ($\downarrow 29$)	0.466 \pm 0.2135** ($\downarrow 47$)

a Data were obtained from Table 6 on page 67 of the study report. The results of the non-fasted animals, sampled on day 93, were omitted from statistical analysis. Percent difference from controls, calculated by the reviewers, is included in parentheses.

* Significantly different from the control group at $p \leq 0.05$.

** Significantly different from the control group at $p \leq 0.01$.

E. SACRIFICE AND PATHOLOGY

1. **Organ weight** - Liver weights (absolute, relative to body, and relative to brain) were increased ($\uparrow 14$ -16%; $p \leq 0.01$) in the 5000 ppm males. Relative (to brain) liver weights were also increased ($\uparrow 9\%$; $p \leq 0.01$) in the 1000 ppm males (Table 4). Relative (to body) liver weights were increased ($\uparrow 12\%$; $p \leq 0.05$) in the 5000 ppm females. Absolute, relative to body, and relative to brain weights of all other organs in the treated males and females were comparable to controls.

Table 4. Selected mean (\pm SD) liver weights in mice treated with RPA 407213 in the diet for up to 90 days.^a

Organ	Dose (ppm)				
	0	50	200	1000	5000
Males					
Terminal body weights	23.9 \pm 0.73	24.3 \pm 1.06	24.1 \pm 1.01	24.3 \pm 0.94	24.2 \pm 0.96
Liver					
absolute (g)	1.02 \pm 0.110	1.04 \pm 0.053	1.04 \pm 0.098	1.09 \pm 0.064	1.16 \pm 0.052** (\uparrow 14)
relative to body (%)	4.22 \pm 0.256	4.24 \pm 0.132	4.36 \pm 0.171	4.43 \pm 0.342	4.85 \pm 0.155** (\uparrow 15)
relative to brain (%)	231.0 \pm 6.01	239.3 \pm 11.01	240.0 \pm 12.14	252.4 \pm 12.33** (\uparrow 9)	268.9 \pm 10.83** (\uparrow 16)
Females					
Terminal body weights	20.5 \pm 0.96	19.9 \pm 0.73	20.5 \pm 0.79	20.8 \pm 0.88	20.0 \pm 0.89
Liver					
absolute (g)	0.87 \pm 0.076	0.80 \pm 0.082	0.87 \pm 0.095	0.91 \pm 0.105	0.95 \pm 0.120
relative to body (%)	4.22 \pm 0.320	4.03 \pm 0.365	4.29 \pm 0.403	4.41 \pm 0.377	4.72 \pm 0.385* (\uparrow 12)
relative to brain (%)	192.4 \pm 16.38	181.9 \pm 22.04	200.5 \pm 24.48	202.9 \pm 15.06	210.9 \pm 25.92

a Data were obtained from Tables 7 through 9 on pages 69-80 of the study report. The results of the animals not fasted overnight before sacrifice on day 93 were omitted from statistical analysis. Percent difference from controls, calculated by the reviewers, is included in parentheses.

* Significantly different from the control group at $p \leq 0.05$.

** Significantly different from the control group at $p \leq 0.01$.

2. Gross pathology - In the 200, 1000, and 5000 ppm males, a dose-dependent increase was observed in the incidence of pale liver (5/10 to 7/10 treated vs 3/8 controls; Table 5). Prominent lobulation of the liver was noted in the 1000 and 5000 ppm females (1 each treated vs 0 controls).

Additionally at 5000 ppm, multiple, moderate, white, pinpoint foci were observed on the liver of one 5000 ppm male (vs 0/8 controls), and black content was observed in the stomach and intestine of one female (vs 0/10 controls); however, these changes were uncorroborated by histopathology and were considered incidental. A dose-dependent increase in the incidence of diffuse corneal opacity (1-4 treated vs 0 controls) was observed in the 200, 1000, and 5000 ppm males; however, in the absence of correlative changes in histopathology, this finding is considered equivocal. There were no other dose-dependent macroscopic observations.

Table 5. Selected macroscopic findings (#affected) in mice treated with RPA 407213 in the diet for up to 90 days.^a

Gross Observation	Dose (ppm)				
	0	50	200	1000	5000
Males					
Number examined	8	10	9	10	10
Liver - Pale	3	3	5	5	7
Eye - Corneal opacity, diffuse	0	0	1	2	4

Females					
Number examined	10	10	10	10	9
Liver - Prominent lobulation	0	0	0	1	1

a Data were obtained from Table 10 on pages 81-83 of the study report.

3. Microscopic pathology - Dose-dependent increases were observed in the incidences of hepatocellular microvacuolation in the 200, 1000, and 5000 ppm males (6/9 to 8/10 treated vs 4/8 controls; Table 6). Additionally, the following microscopic changes were observed at 5000 ppm: (i) diffuse, marked axonal swelling and myelin sheath vacuolation of the sciatic nerve in the males (1/10 treated vs 0/8 controls); (ii) acute inflammatory cell infiltrate in the liver in the females (1/9 treated vs 0/10 controls); and (iii) diffuse, marked thymic atrophy in the females (2/9 treated vs 0/10 controls). One male in each of the treated groups had dark brown pigment-loaded macrophages in the spleen; these findings increased in severity (slight to moderate) with increasing dose. Several other findings were noted at 5000 ppm, such as subcapsular fusiform cell hyperplasia in the adrenal gland in the males and ovarian cysts in the females; however, these observations were considered unrelated to treatment because they were minor in incidence and severity.

Table 6. Selected microscopic findings (#affected) in mice treated with RPA 407213 in the diet for up to 90 days.^a

Microscopic Observation	Dose (ppm)				
	0	50	200	1000	5000
Males					
Number examined	8	10	9	10	10
Liver - Hepatocellular microvacuolation	4	5	6	8	8
Spleen					
Dark brown pigment-loaded macrophages - Total	0	1	1	1	1
Focal, slight	0	1	1	0	0
Focal, moderate	0	0	0	1	1
Sciatic nerve - Axonal swelling and myelin sheets vacuolation					
Diffuse, marked	0	0	0	0	1
Females					
Number examined	10	10	10	10	9
Liver - Acute inflammatory cell infiltrate	0	0	0	0	1
Thymus - Atrophy					
Diffuse, marked	0	0	0	0	2

a Data were obtained from Table 11 on pages 84-94 and Appendix I on pages 151-252 of the study report.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: It was concluded that the LOAEL was 1000 ppm based on decreased cholesterol in the 1000 and 5000 ppm females, increased liver weights in the 1000 ppm males and 5000 ppm animals, and increased incidences of pale appearance of the liver and hepatocellular microvacuolation in the 1000 ppm animals and 5000 ppm males. The NOAEL was 200 ppm.

B. REVIEWER COMMENTS: In the males, liver weights (absolute, relative to body, and relative to brain) were increased (\uparrow 14-16%; $p \leq 0.01$) at 5000 ppm, and relative (to brain) liver weights were increased (\uparrow 9%; $p \leq 0.01$) at 1000 ppm. In the 200, 1000, and 5000 ppm males, dose-dependent increases were observed in the incidence of pale liver (5/10 to 7/10 treated vs 3/8 controls) and hepatocellular microvacuolation (6/9 to 8/10 treated vs 4/8 controls). In the liver in the females, prominent lobulation was noted at 1000 and 5000 ppm (1/10 to 1/9 treated vs 0/10 controls), and acute inflammatory cell infiltrate was observed at 5000 ppm (1/9 treated vs 0/10 controls). Additionally, in the 5000 ppm females, cholesterol was decreased (\downarrow 29-47%; $p \leq 0.05$).

Additionally at 5000 ppm, diffuse, marked axonal swelling and myelin sheath vacuolation was observed in the males (1/10 treated vs 0/8 controls); and diffuse, marked thymic atrophy was observed in the females (2/9 treated vs 0/10 controls). One male in each of the treated groups had dark brown pigment-loaded macrophages in the spleen; these findings increased in severity (slight to moderate) with increasing dose.

Opacity was observed in the eyes of one 5000 ppm female (vs 0/10 controls). A dose-dependent increase in the incidence of diffuse corneal opacity (1/9 to 4/10 treated vs 0/8 controls) was observed in the 200, 1000, and 5000 ppm males; however, in the absence of correlative changes in histopathology, this finding is considered equivocal.

The LOAEL for this study is 1000 ppm (equivalent to 220.17/273.86 mg/kg/day in the males/females) based on mild hepatotoxicity as evidenced by increased liver weights and incidences of pale liver and hepatic microvacuolation in the males and decreased cholesterol and increased incidence of prominent lobulation of the liver in the females. The NOAEL is 200 ppm (equivalent to 44.49/54.13 mg/kg/day in the males/females).

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirements for a subchronic oral toxicity study in the mouse (OPPTS 870.3100b; OECD 408).

C. STUDY DEFICIENCIES: The following deficiencies were noted, but do not change the conclusions of this DER:

Major deficiencies

- Hematological parameters were not examined.
- Organs weights were not obtained for the adrenals, thymus, epididymides, uterus, and ovaries.

Minor deficiencies

- Sorbitol dehydrogenase was not measured.
- The nose and pharynx were not examined microscopically at sacrifice.

